Remission frequency *versus* remission quality in transplant-eligible older patients. Comment on: "Treatment of therapy-related acute myeloid leukemia and acute myeloid leukemia with myelodysplasia-related changes: a comparative analysis of higher-dose intensive 7+3 induction chemotherapy *versus* liposomal cytarabine and daunorubicin"

We read with interest the analysis by Kotsos and colleagues comparing a higher-intensity double-induction 7+3 regimen, which incorporates a second cycle of intermediate-dose cytarabine as delivered in the HOVON-SAKK-Nordic trials, with CPX-351 in older patients with therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes.[1] This is a thoughtful contribution to a genuinely open question. Using reconstructed survival data, the authors report a higher complete remission or complete remission with incomplete recovery (CR/CRi) rate with the double-induction 7+3 regimen (67.8% *vs*. 47.7%) yet similar overall survival (OS) (median 10.1 *vs*. 8.9 months; hazard ratio=0.99, *P*=0.95), with comparable early mortality and transplant rates. Given the relatively low CR/CRi rate in the control arm of the pivotal trial,[2] this is a useful and carefully constructed comparison. We write to highlight one of the study's own results, the post-transplant survival advantage observed with CPX-351, which we found difficult to reconcile with an interpretation of comparable efficacy, and to suggest that a difference in measurable residual disease (MRD) at transplant, not captured in either cohort, may be a relevant explanation.

Among patients who achieved CR/CRi and proceeded to allogeneic hematopoietic cell transplantation (HCT) at comparable rates (54.1% *vs*. 56.2%, *P*=0.88), post-transplant OS favored CPX-351 (median not reached *vs*. 14.4 months, *P*=0.007). As the authors themselves note, the objective of intensive induction is to achieve a deep remission that allows the patient to proceed to transplantation. Viewed through that lens, post-transplant outcomes seem particularly relevant to interpreting an apparent equivalence between induction strategies. In the subgroup most likely to achieve durable disease control, the direction of effect differs from the study's broader interpretation, a tension we believe merits fuller discussion.

This pattern is itself informative. A 20-point CR/CRi advantage that does not translate into longer OS, and that appears to reverse after transplant, raises the possibility that the additional remissions achieved with double-induction differ in quality from those achieved with CPX-351. This interpretation is consistent with the broader CPX-351 experience. *Post-hoc* analyses of the pivotal trial found longer post-transplant survival with CPX-351 across European LeukemiaNet risk subgroups,[3] and the dedicated transplant analysis attributed the post-HCT advantage to lower cumulative incidence of relapse and lower non-relapse mortality.[4] The authors also note that unavailable salvage-therapy data may contribute to the absence of an OS difference; that consideration, however, applies to the whole-cohort comparison and would not obviously account for the reversal observed among patients who had already achieved remission and proceeded to transplantation. Taken together, these data suggest that for the transplant-bound patient, remission depth may be as important as remission frequency.

One biologically plausible explanation is a difference in MRD burden at the time of transplant, although MRD data were not reported for either cohort. A morphological CR/CRi is not equivalent to an MRD-negative remission for transplant purposes: pretransplant MRD positivity is among the strongest predictors of relapse and inferior survival after allogeneic HCT.[5,6] Direct evidence supports this in the relevant population: in a multicenter cohort of older patients with therapy-related AML or AML with myelodysplasia-related changes treated with CPX-351, MRD status, rather than morphological response, predicted OS (20.4 *vs*. 12.9 months for MRD below *vs*. above 10^{-3}) and tracked with post-transplant outcome.[7] A higher morphological remission rate may therefore include a larger proportion of MRD-positive remissions that fare less well after transplantation. In the absence of MRD data, an equivalence interpretation may not fully distinguish "as many remissions" from "as many transplant-enabling remissions," and these are not interchangeable in a population for whom transplant remains the principal curative option.

We recognize that this transplant comparison is a non-randomized subgroup nested within a cross-trial analysis, and that the higher proportion of adverse-risk cytogenetics in the 7+3 cohort (67.6% *vs*. 50.3%) is a candidate explanation for the post-transplant difference. We would note, however, that the 7+3 cohort achieved higher remission rates despite this less favorable cytogenetic profile, so adverse-risk distribution alone may not fully account for its inferior post-transplant survival, which seems at least equally consistent with a difference in remission quality. The cleanest way to resolve the question is prospective: the randomized trial now underway (NCT03897127) would ideally incorporate MRD, reporting post-HCT outcomes by MRD status as well as by induction arm, which would help to establish whether obligatory double-induction truly matches CPX-351 in patients who can be cured. Until such data are available, we would interpret the finding of broadly comparable outcomes with some caution for transplant-eligible patients.

We commend the authors for a rigorous and clinically relevant analysis, and we hope these reflections are useful in sharpening a question that the field now needs to answer.

Authors

Naif I. AlJohani

Adult Hematology and Hematopoietic Stem Cell Transplantation Section, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

Correspondence:
N.I. ALJOHANI - naljohani@kfshrc.edu.sa

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